IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Francisco, Joseph A. et al.

U.S. Serial No: 09/724,406

Filing Date: November 28, 2000

Title: *RECOMBINANT ANTI-CD30 ANTIBODIES AND USES THEREOF*

Commissioner for Patents
Washington, D.C. 20231

PUBLIC PROTEST AGAINST U.S. SERIAL NO. 09/724,406

UNDER 37 CFR § 1.291

(Second Submission)

This protest is being submitted further to the initial Protest submitted against the above-identified application on March 3, 2003 in view of new data that had not been generated at the time of the initial Protest and, thus, which could not have been presented with the initial Protest.

The above-identified U.S. patent application is hereby protested in view of such new data from *in vitro* studies presented herewith and the following references: Pohl et al., 1993, Int. J. Cancer 54:418-425 and Falini et al., 1992, Brit. J. Haematology 82: 38-45. It is noted that these references were published more than one year before the filing date of the '406 Application and, thus, are available as prior art under 35 U.S.C. §102(b). For the Examiner's convenience, a copy of both the '406 Application[1] and the two references are enclosed as Appendices A, B and C, respectively.

The '406 Application claims a method for treating or preventing Hodgkin's Disease (HD) by administering an anti-CD30 antibody that exerts a cytostatic or cytotoxic effect on HD cells. That Application further claims pharmaceutical compositions containing such antibodies. Representative method and pharmaceutical compositions claims in the '406 Application are shown below, corresponding to claims 1 and 20 of the '406 Application as originally filed.

[1] The enclosed copy of the '406 Application serves as the priority document for PCT Publication WO 02/43661 (a continuation-in-part application of the '406 Application) and was obtained as part of the published file history for WO 02/43661.

Exemplary method claim

A method for the treatment or prevention of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment or prevention, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line; and (b) a pharmaceutically acceptable carrier.

Exemplary composition claim

A pharmaceutical composition comprising:

(a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, and is not monoclonal antibody AC10 or HeFi-1 and does not result from cleavage of AC10 or HeFi-1 with papain or pepsin, in an amount effective for the treatment or prevention of Hodgkin's Disease; and

(b) a pharmaceutically acceptable carrier.

The data reported herein pertain to prior art antibodies that inherently possess the claimed properties of specifically binding to CD30 and exerting a cytostatic or cytotoxic effect on a Hodgkin's Disease (HD) cell line. In addition, as discussed herein, one of these prior art antibodies, referred to as HRS-4, has been shown in the prior art by Pohl et al. to be capable of effectively treating Hodgkin's disease in murine models. Therefore, the data reported herein clearly establish that the claims in the '406 Application lack novelty over the teachings of Pohl et al. Furthermore, the data described herein disprove the nexus taught in the '406 Application between anti-CD30 antibodies that possess the claimed properties of exerting a cytostatic or cytotoxic effect on HD cells and antibodies that possess the claimed therapeutic efficacy in treating HD in a subject. Specifically, as shown herein, the anti-CD30 antibody Ber-H2 exhibits a cytostatic or cytotoxic effect on HD cells, but has been shown in the prior art by Falini et al. to be ineffective in treating HD. Therefore, the data provided herein establish that the claimed methods and compositions of the '406 Application are not sufficiently enabled, since the Application fails to provide any accurate guidance as to how to select anti-CD30 antibodies having therapeutic efficacy in treating HD as claimed.

Prior art anti-CD30 antibodies HRS-4 and Ber-H2 inhibit the growth of Hodgkin's cell lines upon cross-linking *in vitro* similarly to the claimed antibodies

According to the '406 Application, antibodies of the invention inhibit the *in vitro* growth of Hodgkin's cell lines upon cross-linking with another antibody (see page 6, lines 1-5, and Example 6.2 at page 51, lines 16-22 of the '406 application). Prior art anti-CD30 antibodies HRS-4 and Ber-H2 were similarly tested *in vitro* to determine whether they too mediate growth inhibition of CD30 expressing tumor cell lines, including HD cell lines, upon cross-linking with another antibody. Using the same *in vitro* cross-linked soluble antibody assays that Applicants employed to select the two exemplified antibodies of the invention, referred to as AC10 and HeFi-1 (*see* Example 6 of the '406 application), it was observed that the prior art anti-CD30 antibodies also demonstrated growth inhibition of CD30 expressing HD cell lines.

As described in the enclosed Declaration by Dr. Robert F. Graziano, the prior art antibodies Ber-H2, HRS-4 and AC-10 were tested for their ability to inhibit growth of CD30 in the following cell lines: L540 (Hodgkin's lymphoma derived cell line with a T cell phenotype), L428 (Hodgkin's lymphoma derived cell line with a B cell phenotype) and Karpas 299 (anaplastic large cell lymphoma derived tumor line). The cross-linking antibody employed was a goat anti-mouse. Ramos cell line (CD30 negative lymphoma) and the anti-murine cross-linking antibody alone were used in control experiments to confirm binding specificity and growth inhibition of the anti-CD30 antibodies.

The cell lines were cultured in flat-bottomed, 96-well tissue culture plates in a final volume of 200 µl/well (in triplicate). The anti-CD30 antibodies were added to the cell lines to a final concentration of 2 µg/ml. Secondary cross-linking antibody was added to a final concentration of 8 µg/ml. After 96 hours, the plates were pulsed with ^{3}H-thymidine (0.5 µCi/well), and incubated for an additional four hours before harvesting and counting on a scintillation counter.

When cross-linked with the secondary antibody, all of the anti-CD30 antibodies inhibited growth of the CD30-expressing L540 cells (Figure 1A), L428 cells (Figure 1B) and Karpas 299 cells (Figure 1C) as shown by a decreased uptake of ^{3}H-thymidine. The cross-linking goat anti-mouse antibody alone did not mediate this growth inhibition. Growth of the CD30 negative lymphoma line, Ramos, was not affected by any of the treatments (Figure 1D). These data demonstrate that the prior art antibodies HRS-4 and Ber-H2 can exert cytostatic or cytotoxic effects on HD cell lines *in vitro*, similarly to the claimed antibodies.

The HRS-4 and Ber-H2 antibodies inhibit *in vitro* growth of CD30-expressing cell lines upon cross-linking

Pohl et al. and Falini et al. describe monoclonal antibodies HRS-4 and Ber-H2, respectively, neither of which is AC-10 or HeFi-1 nor derived therefrom, that bind to CD30. As discussed above, HRS-4 and Ber-H2 also exert a cytostatic or cytotoxic effect on HD cell lines in cross-linking assays that do not involve cells other than HD cells (e.g., L540 and L428 cell lines). Thus, the data provided herewith demonstrate that both prior art antibodies possess the property "exerts a cytostatic or cytotoxic effect on a Hodgkin's disease cell line" in the absence of a cytostatic or cytotoxic agent and in the absence of cells other than HD cells. Moreover, the data was generated using the very growth inhibition assays, which employ cross-linking antibodies, described in the '406 Application and used to select the claimed antibodies.

Thus, the results of the *in vitro* studies described herein clearly indicate that the prior art antibodies HRS-4 and Ber-H2 mediate growth inhibition of CD30 expressing cell lines, including the Hodgkin's cell lines L540 and L428, *in vitro* in the same manner as AC-10 and HeFi-1 and as taught and claimed in the '406 Application (see page 51, lines 16-22 of the '406 application). *In vitro* growth inhibition activity of an anti-CD30 antibody, which can be shown using cross-linking antibodies, was used as the selection criteria by Applicants to identify the prior art antibodies AC-10 and HeFi-1, and is taught in the '406 Application as being a basis by which one of ordinary skill can select other anti-CD30 antibodies capable of treating HD *in vivo*.

Furthermore, Pohl *et al.* show that HRS-4, formulated into a pharmaceutical composition, is effective in treating HD in animal models, as claimed in the '406 Application. Therefore, the, the composition claims and method claims in the '406 Application cannot be deemed patentable under 35 USC 102(b) in light of Pohl et al. (HRS-4), since the HRS-4 antibody exhibits all of the claimed properties. Moreover, the composition claims and method claims in the '406 Application cannot be deemed enabled since, as described below, the selection criteria taught in the '406 Application is not predictive of therapeutic efficacy in treating HD *in vivo*.

Although Ber-H2 possesses the claimed cytostatic or cytotoxic activity it fails to effectively treat HD in patients

Ber-H2, first described in Schwarting, 1989, Blood 74: 1678-89, has been the subject of many clinical trials involving treatment of HD patients. Most of the trials used Ber-H2 linked to

immunotoxin (IT) because naked Ber-H2 failed to successfully treat patients with HD. Falini et al., 1992, Brit. J Haematology 82: 38-45, which is prior art under 35 USC 102(b) against the '406 Application, teaches administration of Ber-H2 without IT to patients for *in vivo* immunohistological study and for assessment of anti-tumor activity. While Ber-H2 was shown bound to Hodgkin's and Reed-Sternberg cells at tumor sites, there was no measurable decrease in the size of these tumor sites during the 40 days of Ber-H2 therapy (see Falini, page 41, right col., last paragraph). Since Ber-H2 demonstrated ability to inhibit growth of HD cell lines upon cross-linking, the clinical study results are contrary to the teachings in the '406 Application, i.e., that an antibody which exhibits growth inhibition upon *in vitro* cross linking, e.g., Ber-H2, is useful for treating HD *in vivo*. Clearly, Ber-H2 has not been successfully used in treating HD in patients.

Based on the Ber-H2 data presented herein and the clinical study results reported in Falini, the invention claimed in the '406 Application would require undue experimentation to practice because, although the data submitted herewith indicate that Ber-H2 inhibits growth of HD cells *in vitro* upon cross-linking with a secondary antibody in a manner similar to antibodies claimed in the '406 Application, Ber-H2 failed to effectively treat HD patients in clinical studies. In order for a claim to be enabled by the specification, there must be sufficient teaching regarding the subject matter of the claims to enable one of ordinary skill in the art to make and use the invention without undue experimentation.

In determining undue experimentation, several factors must be considered as follows. First, the claims in the '406 application are broad, and encompass antibodies that exist in the prior art, since there is no structural limitation to narrow the scope of invention to those antibodies created by Applicant, e.g., chimeric AC10. The nature of Applicants invention, being that it is biotechnological, is inherently unpredictable and complex, and requires a high level of specialized skill to practice. Furthermore, the prior art is replete with examples of naked anti-CD30 antibodies which have failed at providing an efficacious treatment for HD (leading to experimentation with IT-conjugated antibodies), as discussed in the Background section of the '406 Application. In addition, Applicant provides insufficient guidance for selecting the claimed antibodies, i.e., those useful in treating HD. Finally, there is only a single working example employing a modified prior art antibody (AC-10) which demonstrates *in vivo* activity in a murine model.

The data submitted herewith weaken any correlation Applicants believe they have discovered between anti-CD30 antibodies that demonstrate *in vitro* growth inhibition upon cross-linking (i.e., cytostatic or cytotoxic activity) and *in vivo* efficacy. Ber-H2 demonstrated *in vitro* growth inhibition but failed to show *in vivo* efficacy, which suggests a disconnect between the predictability of Applicant's *in vitro* growth inhibition assay for anti-CD30 antibodies to perform efficaciously in Applicant's method of treatments. One of ordinary skill in the art would have to undergo undue experimentation in the form of expensive, time-consuming, and inherently unpredictable clinical trials, i.e., endure undue experimentation, to confirm whether antibodies selected based on the teachings of the '406 Application would actually work in the claimed methods. Although the scope of a claim may encompass inoperable embodiments, the claims of the '406 cannot be found to properly satisfy 35 USC 112, first paragraph, because there is insufficient guidance in the specification for selecting anti-CD30 antibodies having the claimed *in vivo* therapeutic property. Therefore, the claims of the '406 Application which do not require use of chimeric AC-10 or HeFi-1 are not enabled.

The '406 Application

The '406 Application claims a method for using an anti-CD30 mAb to treat or prevent HD, as well as pharmaceutical compositions containing an anti-CD30 mAb (see, *e.g.*, Exemplary claims, *infra*). The '406 Application specifically describes two murine mAbs that bind CD30, *i.e.*, AC10 (a.k.a. C10) and HeFi-1, which were both previously described in the prior art and shown to bind CD30 (see, *e.g.*, Bowen et al., 1993, J. Immunol. 151: 5896-5906 and Hect et al., 1985, J. Immunol. 134:4231-36). In addition, the '406 Application contains data from *in vivo* experiments, including injecting the prior art antibodies AC10 or HeFi-1 i.p. into SCID mice bearing disseminated HD (L540) tumor cells.

Based on the Pohl and Falini references and the data provided herewith, a claim to a method for using a monoclonal antibody that binds CD30 and exerts a cytostatic or cytotoxic effect on HD cells to treat or prevent HD, as claimed in the '406 application, is clearly anticipated under 35 USC 102(b). Similarly, a claim to a pharmaceutical composition containing such an anti-CD30 mAb, or containing such an anti-CD30 mAb that "is not monoclonal antibody AC10 or HeFi-1" (see *e.g.*, claim 20) is also clearly anticipated by both Pohl et al and Falini et al. as supported by the data presented herein. Indeed, both the Pohl and Falini references teach anti-CD30 antibodies, other than AC10 and HeFi-1, which specifically bind to CD30.

Similarly, the added claim limitation, whereby the anti-CD30 antibody is conjugated to a cytotoxic agent, in certain dependent claims of the '406 Application (see *e.g.*, claim 4), is not novel. Indeed, at page 2 (lines 8-10) of the '406 Application, the Applicants explicitly acknowledge that it was shown in earlier clinical trials that "a toxin (saporin) was chemically conjugated to the antibody Ber-H2 and all four patients demonstrated rapid and substantial reductions in tumor mass" (Falini et al., 1992, Lancet 339:1195-1196).

Moreover, the additional dependent claim limitations reciting, for example, that (i) the antibody is "human, humanized or chimeric" (see *e.g.*, claim 2), that (ii) chemotherapy is administered (see *e.g.*, claim 3), that (iii) the antibody is fused to a second protein which is not an antibody (see *e.g.*, claim 5), that (iv) the cytotoxic or cytostatic effect is determined by a particular thymidine incorporation assay (see e.g., claim 7), or that (v) the Hodgkin's Disease cell line is L428, L450, HDLM2 or KM-H2 (see *e.g.*, claim 37), are all obvious in view of the submitted data and Pohl et al. and Falini et al. references. These limitations encompass known technologies available in the art at the time of the filing of the '406 Application.

Related Applications

Although this protest is filed against the '406 Application, the arguments presented herein regarding the teachings of the Pohl and Falini references in light of the present data are equally applicable to applications related to the '406 Application that similarly claim methods of using, or compositions containing, antibodies that bind to CD30 and exert a cytostatic or cytotoxic effect on HD tumor cells. Thus, this protest is also made against such related applications, if pending. For example, a continuation-in-part application of the '406 Application has been published as PCT Publication WO 02/43661, which PCT application designates the United States. Claim 1 of WO 02/43661 recites (emphasis added):

A method for the treatment or prevention of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment or prevention, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent, respectively; and (b) a pharmaceutically acceptable carrier.

First, it is noted that the underlined phrase does not find support in the '406 Application and thus a claim in a U.S. application corresponding to claim 1 of WO 02/43661 would not be entitled to the priority date of the '406 Application. Furthermore, the underlined phrase does not impart novelty to the claim over the cited references in light of the present data since the anti-CD30 antibodies HRS-4 and Ber-H2 exerted a cytostatic or cytotoxic effect on HD cells in the absence of conjugation to a cytostatic or cytotoxic agent.

CONCLUSION

It is therefore respectfully requested that the Examiner for U.S. Application Serial No. 09/724,406, and any related cases thereto, consider the references Pohl et al., 1993, Int. J. Caner 54:418-425 and Falini et al., 1992, Brit. J. Haematology 82: 38-45 in conjunction with the instant protest and data presented herein during examination. A finding of unpatentability of the claims based on the data and references is solicited.

Respectfully submitted,

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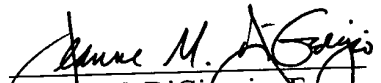

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